REMARKS

The Applicants acknowledge the courtesy extended by Examiner Royds and Supervisory Examiner Marschel during the October 15, 2008 telephonic interview with the undersigned. The written description rejection was discussed during the interview. The Applicants understand that the Examiners tentatively agreed that claims reciting a pharmaceutical combination wherein each dosage formulation releases a fixed ratio of d- to l-amphetamine may be sufficiently described in the specification.

I. Status of the claims

Claims 1-16, 18-21 and 24-29 were pending before this amendment. Claim 14 has been canceled. Claim 26 has been amended to provide antecedent basis. Claims 1 and 16 have been amended to recite that each dosage formulation of the pharmaceutical combination releases a fixed ratio of amphetamine isomer. Support for the claim amendments relating to administering fixed release ratio dosage forms can be found in the specification as follows:

- "A constant d/l ratio may be also present during a period or from one period to the next, as long as said periods are followed by a later period wherein the l/d ratio is increased." Specification, p. 6, ll. 11-13. This embodiment can be achieved by administering a dosage form having a fixed (i.e., constant) release ratio followed later in the day by a dosage form having a fixed release ratio with a higher l:d ratio than the earlier dosage form.
- "This invention includes all possible regimens of administering the two enantiomers of amphetamine, e.g., ... all combinations of the two enantiomers ..." Specification, p. 5, ll. 13-15. Thus, known formulations which release a fixed ratio of d-to l- amphetamine (e.g., 3:1 in ADDERALL), and new amphetamine formulations produced using conventional technology (generally described and specifically exemplified in the specification) are encompassed by the present invention.

- An embodiment is disclosed wherein only d-isomer is administered early in the day (necessarily a fixed release ratio because only one isomer is present) and only l-isomer later in the day (likewise, a necessarily fixed release ratio). Specification, p. 5, ll. 18-21.
- "[T]he doses of each isomer can be administered in the most varied ways, e.g., each can be administered separately ... " Specification, p. 5, ll. 25-26.
- An embodiment is disclosed wherein ADDERALL (a commercial formulation having a d:l ratio of 3:1) or "any other dose of d/l greater than one" is administered early in the day and a later dose has a ratio of l:d that is higher than the ratio in the dosage form administered early in the day. Specification, p. 5, ll. 27-33.
- A blister pack according to the present invention can include a two-compartment pack wherein the first dose is ADDERALL (1:3 l- to d-amphetamine ratio) immediate release tablets or immediate release tablets of d-amphetamine only and the second dose comprises l:d isomer ratios of 1/1, 2/1, 3/1, 4/1 or only l-isomer. P. 39, ll. 1-14.
- *See also,* p. 7, ll. 11-21 describing examples of suitable regimens, e.g., "the first dose having amounts of l and d-isomers in a molar ratio of 1/3 and the subsequent dose having a ratio of 3/1."

Claims 1 and 16 have also been amended to change "dosage form" to "dosage formulation." These amendments clarify that the recited greater than one dosage formulation requires dosage formulations containing different ratios of d- to l- amphetamine isomers, and not different delivery systems (e.g., a tablet and a capsule).

II. Rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-16, 18-21 and 24-29 have been rejected under 35 U.S.C. § 112, first paragraph, written description. According to the Examiner, the specification fails to adequately

describe "the specific structure(s), material(s) or act(s) that are responsible for effecting the function of the combination as instantly claimed" (*see* Office Action, page 4).

Independent claims 1 and 16 have been amended to clarify that the claimed release ratio profile (i.e., the ratio of l- to d- amphetamine released from the pharmaceutical combination in a time period later in the day is higher than the ratio released from the combination at a time period earlier in the day), is achieved by a combination of greater than one dosage formulation, wherein each dosage form releases a fixed ratio of isomer.

The specification states that a: "'Pharmaceutical combination' refers, for example, to two or more entities ... which cooperate on administration to achieve the release properties of this invention." Specification, p. 5, ll. 19-24. Additional support for the claim amendments is provided in the specification. *See,* section I, above. Thus, a pharmaceutical combination according to the invention includes at least two formulations having fixed, but different, release ratios of d- to l- amphetamine. Thus, for example, a first formulation which releases a fixed ratio of d- to l- amphetamine in the morning and a second formulation which releases a fixed ratio of d- to l- amphetamine in the afternoon of the same day falls within claim 1 when the ratio of d- to l- amphetamine released from the second formulation is less than the d- to l- amphetamine released from the first formulation.

Such fixed release ratio combinations are described in the specification in the disclosure of known commercial formulations, the general disclosure that formulations to achieve the claimed invention can be made using conventional technology, and in the formulations disclosed in the examples. *See,* section I, above; specification, p. 10, l. 20 to p. 20, l. 14 (disclosing conventional technology and materials that can be used to produce a formulation for use in a pharmaceutical combination according to the invention); specification, Examples 6-11 disclosing formulations that can be used in a pharmaceutical combination according to the invention.

The amended claims do not require description of a single formulation in which the release ratio of d- to l- amphetamine changes through the course of a day. The claims do require a combination of formulations which result in change in the d- to l- amphetamine through the course of a day. This latter requirement can be satisfied by formulations having fixed isomer release ratios as instantly claimed. Methods for making such formulations were well known in the art and are disclosed in the specification.

For the reasons stated above, the claims as amended are adequately described in the specification. Thus, this rejection should be withdrawn. It is the Applicants understanding that Supervisory Examiner Marschel and Examiner Royds agreed during the interview that a combination comprising fixed release ratio amphetamine formulations is adequately described in the specification.

III. Rejections under 35 U.S.C. § 112, second paragraph

A. Claim 14 has been rejected under 35 U.S.C. § 112, second paragraph as indefinite because it is unclear how a single dosage form may be used to provide both earlier and later periods when independent claim 1 requires greater than one dosage form. Claim 14 has been canceled. Accordingly, this rejection is moot.

B. Claim 26 has been rejected under 35 U.S.C. § 112, second paragraph as indefinite because there is insufficient antecedent basis for "the second unit dose." Claim 26 has been amended to replace "the second unit dose" with "the later unit dose." Claim 25 provides an antecedent basis for the claim amendment. Thus, this rejection should be withdrawn.

IV. Rejections under 35 U.S.C. § 103(a)

Claims 1-16, 18-21 and 24-29 have been rejected under 35 U.S.C. § 103(a) as obvious over Patrick et al., Human Psychopharm. 1997;12:527-546 in view of WO 2002/039998 (Epstein), U.S. Patent No. 6,322,819 (Burnside), STN Registry No. 156-34-3, and Tulloch et al., Pharmacother. 2002;22(11):1405-1415.

Referring back to previous Office Actions, the Examiner contends that Patrick in view of Epstein discloses that "the l-isomer of amphetamine was known to have enhanced efficacy and reduced side effects (i.e., addiction) and compositions of both the l-isomer (either enriched for l-isomer or containing l-isomer alone), as well as compositions of the l- and d-isomers with more d- than l- isomer, were both known in the art for the treatment of ADHD." Office Action dated November 19, 2007. According to the Examiner, determination of the optimum dosage regimen to treat ADHD is routine in the art, and the '819 patent discloses the claimed dosage forms. Further, the Examiner contends that Epstein discloses that l-amphetamine has fewer addictive properties and greater memory enhancing effects compared to d-amphetamine, and Tulloch discloses that the d/l ratio in ADDERALL® is 3:1. The Examiner concludes that in light of these disclosures, it would have been obvious to one of ordinary skill in the art to modify the composition disclosed in Patrick to include more l- than d- isomer.

Independent claims 1 and 16 recite: "wherein the molar ratio of l-amphetamine to d-amphetamine released from the pharmaceutical combination in a time period later in the day is higher than said ratio released therefrom in a time period earlier in the day." A "wherein" clause is a limitation to a claim when it states a condition that is material to patentability. MPEP 2111.04. Here, the "wherein" clause limits the invention to a pharmaceutical combination that releases a higher ratio of l- to d- amphetamine later in the day compared to a time earlier in the day. The Federal Circuit held that a wherein clause was properly construed by the district court to limit the genus "an antigen on nonmalignant, immature human marrow cells," recited in the body of the claim, to one specific antigen. *Johns Hopkins University v. Cellpro, Inc.,* 152 F.3d 1342, 47 USPQ2d 1705, 1708, 1710, 1716 (Fed. Cir. 1998). Consistent with the holding in *Johns Hopkins*, here the wherein clause narrows the universe of pharmaceutical combinations comprising d- and l- amphetamine to those having the recited release ratio profile. Thus, this wherein clause is material to patentability and should be considered a claim limitation.

Patrick discloses that:

- "the rationale for inclusion of the levo isomer remains unclear" (Patrick, abstract);
- Dextroamphetamine is a first or second line treatment for ADHD (Patrick, p. 528, 539);
- Dextroamphetamine is more frequently efficacious than levoamphetamine. "Accordingly, levoamphetamine is not a marketed drug in its own right" (Patrick, p. 536);

Patrick discusses both dextro- and levo- amphetamine, and concludes that: "Methylphenidate, dextroamphetamine, and pemoline are all efficacious in the treatment of ADHD... " (Patrick, p. 539 – conclusion). Levoamphetamine is noticeably missing from the listed efficacious treatments.

Thus, Patrick promotes the use of dextroamphetamine for the treatment of ADHD. Patrick recognizes that levoamphetamine is present as a minor component of ADDERALL, but states that the rationale for its inclusion is unclear. At most, Patrick suggests that levoamphetamine may be useful in the treatment of an undefined subpopulation of ADHD patients (Patrick, p. 536). Patrick does not disclose or suggest taking two different amphetamine formulations during the course of a day. Further, Patrick does not disclose or suggest using a pharmaceutical combination wherein the released molar ratio of l- to d- amphetamine is increased at a time later in the day relative to a time earlier in the day.

Epstein discloses that l- amphetamine (R-(-)-amphetamine) is: (1) at least 4 times more effective as a memory enhancer than d-amphetamine (S-(+)-amphetamine) (Epstein, p. 26, ll. 29-32) and (2) not addictive in contrast to d-amphetamine, which is addictive (Epstein, p. 26, ll. 29-30). Epstein further discloses pharmaceutical compositions comprising several-fold more l-amphetamine than d-amphetamine, or only l-amphetamine. *See, e.g.,* Epstein, p. 9, ll. 5-8. Epstein does not disclose or suggest taking two different amphetamine formulations during the course of a day. Further, Epstein does not disclose or suggest using a pharmaceutical

combination wherein the released molar ratio of l- to d- amphetamine is increased at a time later in the day relative to a time earlier in the day.

Burnside discloses mixed amphetamine salt pharmaceutical compositions comprising both d- and l- isomers. Burnside does not disclose the benefits, or detriments, of one isomer over the other. Burnside does not disclose or suggest taking two different amphetamine formulations during the course of a day. Further, Burnside does not disclose or suggest a pharmaceutical combination wherein the released molar ratio of l- to d- amphetamine is increased at a time later in the day relative to a time earlier in the day.

STN Registry File (Registry No. 156-34-3) discloses chemical names and the chemical structure of l-amphetamine. This registry does not disclose or suggest anything about d-amphetamine, or pharmaceutical combinations wherein the release ratio of d- to l-amphetamine changes at a time period later in the day relative to a time period earlier in the day.

Tulloch discloses experiments to assess the bioavailability of ADDERALL and ADDERALL XR. Each of these formulations provides a fixed release ratio of d-to l-amphetamine (3:1). According to Tulloch, previous studies showed that while most children respond to either isomer, some children respond only to d-amphetamine and some respond only to l-amphetamine. Tulloch, p. 1406. Thus, Tulloch may provide a rationale for administering a formulation containing both the d- and l- isomer. Tulloch does not disclose or suggest a pharmaceutical combination wherein the released molar ratio of l- to d- amphetamine is increased at a time later in the day relative to a time earlier in the day.

In summary, no combination of the references discloses or suggests a pharmaceutical combination wherein the released molar ratio of l- to d- amphetamine is increased at a time later in the day relative to a time earlier in the day. Accordingly, this rejection should be withdrawn.

V. Obviousness-type double patenting rejection

Claims 1-15 and 24-26 have been rejected for obviousness-type double patenting over claims of U.S. Patent Nos. 6,605,300; 6,322,819; 6,913,768; and U.S. Application Nos. 11/091,011; 10/758,417; and 11/030,174. Applicants' request that this rejection be held in abeyance until allowable subject matter has been identified.

Conclusion

No new matter has been added by these amendments. In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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